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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 18

Application Number: 09/210,995
Filing Date: December 15, 1998
Appellant(s): Loosmore et al.

M.I. Stewart
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed October 16, 2000.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

Claim 22 has been amended subsequent to the final rejection.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-24 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,506,139 Loosmore et al. 4-1996

Barenkamp, S.J. "High Molecular Weight Surface Proteins of Non-Typeable Haemophilus." WO 97/36914. October 9, 1997.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barenkamp et al., (WO 97/36,914) in view of Loosmore et al. (US Patent 5,506,139). Barenkamp et al.(WO 97/36,914), teach high molecular weight (HMW) surface proteins of non-typeable Haemophilus. The high molecular weight surface proteins of non-typeable *Haemophilus influenzae* which exhibits immunogenic properties and genes encoding for immunodominant high molecular weight proteins, HMW1, HMW2, HMW3 and HMW4. HMW3 and HMW4 show considerable homology to HMW1 and HMW2 thus HMW3 and HMW4 are also likely to function as adhesins (page 18 lines 14-17). These HMW proteins are related to filamentous hemagglutinin surface proteins, wherein these proteins cause an increased antibody response (page 5 lines 30-35). The immune response to these proteins may be either humoral or a cell-mediated (page 7 lines 18-25). The invention teaches an immunogenic composition comprising the novel high molecular weight protein or synthetic peptides along with a pharmaceutically acceptable carrier for in vivo administration to a host (page 6 lines 20-27). The immunogenic

composition may comprise at least one other immunogenic or immunostimulating material and at least one adjuvant (page 7 lines 1-5). Barenkamp et al.(WO 97/36,914), teach a long list of suitable adjuvants including aluminum phosphate and aluminum hydroxide (page 7 lines 6-17). The high molecular weight proteins can be produced recombinantly (page 10 lines 21-25) and the HMW1 and HMW2 have an apparent molecular weight of 125 and 120 kDa respectively when produced from non-typeable *Haemophilus* (page 15 lines 21-24); while HMW3 and HMW4 have apparent molecular weights of 125 and 123 kDa from non-typeable *Haemophilus*. One example illustrates the use of HMW antigens composed in an immunogenic composition containing 40ug of HMW protein and Freund's adjuvant, the mixture was administered to a host (chinchillas) infected with *Haemophilus influenzae* causing otitis media (pages 47-48 lines 29-33). Barenkamp et al.(WO 97/36,914), teach complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine, hepatitis B virus antigen and others (page 24-25 lines 7-10). Finally, Barenkamp et al's.(WO 97/36,914), data teach that the adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable *H. influenzae* vaccine (page 49 lines 15-19). Barenkamp et al.(WO 97/36,914), however do not teach the use of a different antigen of H.*influenzae* which is not an adhesin in an immunogenic composition.

Loosmore et al., teach an analog of *Haemophilus* Hin47 with reduced protease activity. The Hin47 heat shock protein is immunologically conserved among strains of *Haemophilus influenzae* and is reported to have utility in vaccination against disease caused by *H. influenzae* or other bacterial pathogens that produce Hin47 or proteins capable of rasing antibodies specifically reactive with Hin47 (col. 2 lines 16-21). The Hin47 protein is a protein which is a outer membrane protein with a molecular weight of about 47Kd (col. 2 lines 4-6). Therefore, Loosmore et al., teach that it would be advantageous to provide analogs of Hin47 that are substantially reduced in proteolytic activity for use as an antigen or to be included in other immunogenic preparations (col. 2 lines 29-34). The isolated and purified adhesin analog has decreased protease activity which is less than about 10% of natural Hin47, yet still retains substantially the same immunogenic properties, where at least one amino acid contributing to protease activity may be deleted or replaced by a different amino acid to produce reduced activity (col. 2 lines 44-54). "The at least one deleted or replaced amino acid may be selected from amino acids 195-201 of Hin47, and specifically may be Serine-197, which may be deleted or replaced by alanine. In addition, the at least one deleted or replaced amino acid may be Histidine-91 and may be deleted or replaced by alanine or lysine or arginine. Further, the at least one deleted or replaced amino acid may be Asparagine-121 and may be deleted or replaced by alanine or glutamic acid" (col. 2

lines 56-64). An immunogenic composition comprising an immuno-effective amount of Hin47 analog may be formulated as a vaccine for *in vivo* administration to a host; including a human to confer protection against diseases caused by a bacterial pathogen, such as *Haemophilus influenzae* (col. 3 lines 47-59). The immunogenic composition may further comprise at least one other immunogenic or immunostimulating material such as an adjuvant, and may be contained within a live vector such as a pox virus, salmonella, poliovirus, adenovirus, vaccinia or BCG (col. 3-4 lines 60-2). The analogs may be used as carrier proteins to make conjugate vaccines against antigenic determinants unrelated to Hin47 including pathogenic bacteria (col. 7 lines 15-18 and 40-51). The Hin47 vaccines elicit an immune response which produce antibodies including anti-Hin47 antibodies, and opsonizing or bactericidal antibodies (col. 8 lines 20-31). The Hin47 analogs may be prepared with pharmaceutically acceptable carriers or adjuvants such as aluminum hydroxide or phosphate and should be administered in dosage ranges readily determinable by one skilled in the art (col. 8-9 lines 33-6). Vaccines can be combined with material from various or the same pathogen or from various strains of the same pathogen or from combinations of various pathogens (col. 9 lines 14-20). Example 10 illustrates the comparative immunogenicity of a Hin47 analog in mice, while example 11 illustrates the immunoprotective

properties of the Hin47 analog. Table 2 shows the protective ability of anti-Hin47 mutant antiserum against *H.influenzae* infant rat model of bacteremia.

One would expect a reasonable level of success by combining the well known HMW adhesin proteins and the well known Hin47 analogs in a multi-component immunogenic composition since both Barenkamp et al.(WO 97/36,914), and Loosmore et al., teach the use the these antigens in immunogenic compositions against *Haemophilus influenzae*. Furthermore, both Barenkamp et al.(WO 97/36,914), and Loosmore et al., teach the use of adjuvants; the addition of antigenic components; and methods for immunizing a host against disease caused by an infection with *H. influenzae* comprising administration of the immunogenic composition. No more than routine skill was required at the time of appellants invention to combine two well known compositions, i.e., two different antigens of *H.* influenzae, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for that very same purpose of providing an immunogenic composition.

Therefore it would have been obvious at the time of appellant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, wherein one is a heat shock protein as taught by Loosmore et al., and the other is a high molecular weight adhesin protein, HMW1 or HMW2 which is an important

protective antigen as taught by Barenkamp et al.(WO 97/36,914), because Loosmore et al., teaches that analogs of Hin47 with reduced protease activity from *Haemophilus influenzae* are useful in vaccination against diseases caused by *H. influenzae* or other bacterial pathogens and these proteins are capable of eliciting protective opsonizing or bactericidal antibodies.

(11) Response to Arguments

Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barenkamp et al., (WO 97/36,914) in view of Loosmore et al. (US Patent 5,506,139) is maintained. Appellants argues that there is no suggestion that to combine the references since the Barenkamp et al., lacks a specific teaching to combine the mutant Hin47 protein with the High Molecular Weight (HMW) protein in an immunogenic composition.

In response to appellant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

However, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a

spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). See In re Geiger, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987) ("Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water

In this case, it would have been obvious at the time of appellant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, where one is a well known high molecular weight adhesin protein, HMW1 or HMW2, which are important protective antigens that should comprise one component of a multi-component non-typeable *H. influenzae* vaccine as taught by Barenkamp et al.(WO 97/36,914), in combination with the analog of Hin47 which is a non-proteolytic heat shock protein with substantially reduced proteolytic activity useable in other immunogenic preparations as taught by Loosmore et al.

Appellant argues that the references have been taken out of context because the passages in Barenkamp et al., are discussing certain materials which may be used as adjuvants in the HMW containing immunogenic compositions and not the Hin47 may be combined with the HMW proteins of Barenkamp et al. Appellants cites specific passages from the previous office actions stating that Barenkamp et al.,teach: targeting molecules used in combination with immunogenic compositions that include fragments of bacterial toxins; immunogenic compositions comprising at least one other immunogenic or immunostimulating materials and at least one adjuvant; and complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine and hepatitis B virus antigen and others; but does not teach combining the Hin47 protein.

However, claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barenkamp et al., (WO 97/36,914) in view of Loosmore et al. (US Patent 5,506,139). Therefore, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re*

Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). No more than routine skill was required at the time of appellants invention to combine two well known antigens of *H.* influenzae, an adhesin and a heat shock protein, since the prior art shows that both can elicit an immunogenic response in a host, both are useful to provide protection against a *H. influenzae* infection, both are useful in immunogenic composition in combination with other immunostimulating antigens. Accordingly, both are useful for the same purpose, to form an immunogenic composition to be used for that very same purpose. Appellant has provided no scientific data teaching away from the combination of two well known *H. influenzae* antigens. Appellant neither argues, nor shows scientific data teaching unexpected results.

Therefore it would have been obvious at the time of appellant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, encompassing a protective Hin47 analog protein as taught by Loosmore et al., and a protective high molecular weight adhesin protein, as taught by Barenkamp et al.(WO 97/36,914), because Loosmore et al., teaches that analogs of Hin47 useful in immunogenic compositions are capable of being combined with a variety of other antigens.

Appellant argues that there is no indication that Barenkamp et al., teaches that adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable H.influenzae vaccine. However, Barenkamp et al., teach an immunogenic composition comprising a HMW protein and at least one other immunogenic or

immunostimulating material and at least one adjuvant (page 7 lines 1-5). Barenkamp et al.(WO 97/36,914), teach complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine, hepatitis B virus antigen and others (page 24-25 lines 7-10). Finally, Barenkamp et al's.(WO 97/36,914), data teach "..that HMW adhesin proteins are potentially important protective antigens which may comprise one component of a multi-component NTHI (non-typeable *H. influenzae)* vaccine (page 49 lines 15-19).

Appellant argues that there are important consideration when combining antigens in an immunogenic composition, such as the possibility of impairing or adversely affecting the respective immunogenicities and appellant's results could not have been predicted in advance from the information provided in Barenkamp et al, and Loosmore et al.

In response to appellant's arguments, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). One of ordinary skill would expect a reasonable level of success by combining the well known HMW adhesin proteins and the well known Hin47 analogs in a multi-component immunogenic composition since both Barenkamp et al.(WO

97/36,914), and Loosmore et al., teach the use of these antigens in immunogenic compositions against *Haemophilus influenzae* infection. No more than routine skill would have been required when both Barenkamp et al.(WO 97/36,914), and Loosmore et al., teach the additional use of adjuvants; the addition of antigenic components; and methods for immunizing a host against disease caused by an infection with *H. influenzae* comprising administration of different antigens of *H.influenzae* in an immunogenic composition.

Appellant again argues that there is no motivation provided from the disclosure of Barenkamp et al., to select the non-proteolytic analog of Hin47 protein of Loosmore et al.., and there is no motivation to select the non-proteolytic analog of Hin47 for the purpose that the appellants make the selection. However, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). Furthermore, it would have been obvious to one of skill in the art at the time of appellant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, wherein one is a heat shock protein as taught by Loosmore et al., and the other is a high molecular weight adhesin protein, HMW1 or HMW2 which is an important protective antigen as taught by Barenkamp et al.(WO 97/36,914), because Loosmore et al., teach

that analogs of Hin47 elicit an immune response capable of producing anti-Hin47, opsonizing or bactericidal antibodies, and provides data that shows Hin47 analogs provide protective ability.

Appellant's request a request for reconsideration of the final action, however, as stated in the advisory action appellants arguments were not found persuasive. Appellants argue that there is no suggestion to combine the references. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As previously stated, it would have been obvious at the time of applicant's invention to have an immunogenic composition to confer protection against *Haemophilus influenzae* comprising at least two different antigens, where one is a high molecular weight adhesin protein, HMW1 or HMW2, since Barenkamp et al.(WO 97/36,914), teach that adhesin proteins are important protective antigens which should comprise one component of a multi-component non-typeable *H. influenzae* vaccine and the other component as taught by Loosmore et al., is an analog of Hin47 because the Hin47 analog can be used as a component in an immunogenic

composition and can elicit anti-Hin47, opsonizing or bactericidal antibodies to provide an immunogenic response to *H.influenzae*. Furthermore, one would expect a reasonable level of success by combining the well known HMW adhesin proteins and the well known Hin47 analogs in a multi-component immunogenic composition since both Barenkamp et al.(WO 97/36,914), and Loosmore et al., teach the use the these antigens in immunogenic compositions against *Haemophilus influenzae*.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Ja-Na Hines
August 13, 2001

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